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CRYSTALLINE IDENTITY OF FERRIC MALTOL MANUFACTURED BY WBCIL: WHY POLYMORPH 'A' MUST BE THE REGULATORY STANDARD FOR THE PURE ACTIVE PHARMACEUTICAL INGREDIENT

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ABSTRACT

Ferric Maltol is a non-salt-based oral iron replacement therapy gaining recognition for its superior tolerability and optimized absorption. The efficacy and regulatory standard of this active pharmaceutical ingredient (API) are intrinsically linked to its solid-state properties, specifically its polymorphic forms. This article utilizes previously published analytical data, primarily focused on the materials designated by the manufacturer West Bengal Chemical Industries Ltd., Kolkata, India (WBCIL) as Polymorph 'A' and Polymorph 'S'. Polymorph 'A', characterized by an intrinsic melting point of approximately 300.2∘C and distinctive X-ray diffraction (XRD) peaks at 15.58∘ and 22.56∘ (2-theta). Polymorph 'S' exhibits a lower melting point of 276.56∘C and unique diffraction peaks. We conclude that Polymorph 'A' must be formally maintained as the singular, scientifically rigorous regulatory standard for the pure API identity, thereby ensuring consistency in quality control and rooting all stability and bioavailability claims in its well-characterized core structure.

KEYWORDS: Ferric Maltol, Polymorphism, Solid-state Characterization, Polymorph A, Polymorph S, X-ray Diffraction (XRD).

1. INTRODUCTION

Ferric Maltol, an oral iron replacement therapy for conditions like iron deficiency anaemia associated with inflammatory bowel disease, has gained prominence for its optimized absorption and minimal gastrointestinal toxicity.[1] Its efficacy is intrinsically linked to its solid-state properties, as the existence of various polymorphic forms dictates crucial parameters such as solubility, stability, and bioavailability. The pharmaceutical manufacturer, West Bengal Chemical Industries Ltd. Kolkata, India (WBCIL), has been a key contributor to the advancement of this active pharmaceutical ingredient (API), disclosing its distinct solid-state designation of Polymorph 'A'.[2]

Molecular polymorphism profoundly impacts the pharmacological profile of a drug molecule. Different polymorphs possess distinct thermodynamic properties (such as crystal lattice energy), which directly translate into differences in key parameters like solubility and dissolution rate.[3] Since a drug must be dissolved to be absorbed, these solid-state variations are a primary determinant of a drug's bioavailability—that is, the fraction of the administered dose that reaches the systemic circulation.[4] Consequently, controlling the precise polymorphic form is a mandatory regulatory requirement to ensure consistent quality, predictable efficacy, and patient safety.[5]

We have previously published our research article stating how WBCIL formulates the commercial API of Ferric Maltol in Polymorphic Form 'A', which is characterized by a melting point of approximately 300.2∘C.[2] The solid-state identity of Form 'A' is confirmed by X-ray

diffraction (XRD) analysis, showing characteristic peaks at 15.58∘ and 22.56∘ (at 2-theta degree).[1] The importance of Ferric Maltol Polymorph 'A' is highlighted by its role as the fundamental crystalline structure. This polymorph is significant as it represents the intrinsic standard for the pure Ferric Maltol crystal.[3] Polymorph A is a non-salt-based oral iron formulation designed to overcome the severe gastrointestinal (GI) side effects common with conventional oral iron salts, thereby promoting better compliance.[6] Conventional ferrous salts are known to be poorly tolerated, often causing side effects like nausea, vomiting, diarrhoea, and abdominal pain, which frequently lead to patients discontinuing treatment. This occurs because up to 90% of ferrous iron is unabsorbed and undergoes oxidation in the gut, generating reactive oxygen species that can cause mucosal damage.[7] Ferric maltol Polymorph A is designed to reduce these adverse events by providing stable iron delivery that is more efficiently absorbed, thereby minimizing the amount of unabsorbed free iron available to cause mucosal toxicity and disrupt the gut microbiota.[8] In clinical trials, the rate of GI adverse events with Polymorph A has been low and, in some cases, even similar to that seen with placebo. The favourable tolerability profile of this form of Ferric Maltol makes it a valuable alternative for people who are intolerant of oral ferrous iron products.[9] Studies have shown that Polymorph A is well-tolerated over long-term treatment for up to 64 weeks, which is crucial for persons with chronic underlying conditions such as IBD and CKD requiring extended iron replacement therapy.[10] For people who cannot tolerate conventional oral iron, IV iron is the traditional alternative. However, Ferric Maltol Polymorph A offers a non-invasive, more convenient oral option for them. While IV iron offers faster correction of iron stores, it carries risks such as hypersensitivity reactions and requires administration in a clinical setting, making Ferric Maltol Polymorph A as a less logistically challenging and lower-risk alternative.[11]

Also, there are other stabilised forms of Ferric Maltol with characteristic triple-layer structures. These are Polymorphic Form I, Form II, Form III, and Form IV; each distinguishable by characteristic powder X-ray diffraction (PXRD) patterns, thermal behavior, and stability profiles. Form I represents the thermodynamically stable crystalline phase under ambient conditions; it is non-hygroscopic, displays a well-defined PXRD fingerprint, and is typically chosen for pharmaceutical development because of its superior long-term stability. Form II is a metastable crystalline modification that can convert to Form I upon exposure to moisture, temperature variation, or mechanical stress. It shows slightly higher apparent solubility but lower physical stability. Form III is described as a partially amorphous or disordered crystalline form with enhanced dissolution and hydration tendency, often obtained during rapid precipitation or incomplete crystallization. In contrast, Form IV corresponds to a hydrated crystalline variant (a pseudopolymorph) containing coordinated water molecules within its lattice, which confers distinctive endothermic transitions on differential scanning calorimetry (DSC) analysis. These polymorphic transformations are reversible under controlled drying or rehydration, underscoring the complex solid-state behavior of ferric trimaltol and the need for precise control of crystallization parameters during formulation and storage.[10,11]

WBCIL also manufactures Polymorph S which comprises a characteristic triple-layer structure that incorporates L-Lysine and Ascorbic Acid into it. This Polymorph S has been detailed in the granted patent of WBCIL.[2]

2. Ferric Maltol Polymorph 'A' as the Pure API Standard

Polymorph 'A' is of critical significance because it represents the intrinsic standard for the pure Ferric Maltol crystal.[12,13] Its analytical characteristics, specifically its higher melting point and its clear crystallographic fingerprint (XRD 2-theta peaks) accurately reflect the crystal lattice of the API. This intrinsic form must be maintained as the regulatory standard for the pure API identity in quality control.[14] Therefore, all stability and bioavailability claim for the drug are rooted in the well-characterized, stable core crystal structure of Polymorph 'A'.[15] Focusing on Polymorph 'A' ensures a scientifically rigorous and consistent basis for the identity of the API.

3. Data Sources and Analytical Methodology

This article employs an analytical methodology based on our previously published article on Ferric Maltol Polymorph A.[1] This study is focused on the analysis of significance of Ferric Maltol Polymorph A to represent this form as the pure API standard in manufacturing industry. No new experimental data was generated for this study. Data points extracted included the physical description, thermal characteristics, and crystallographic parameters of Polymorph A, and also Polymorph S, as this form had been described in the patent document of WBCIL.[2]

The methodology involved a three-step process of data extraction, analysis, and scientific reconciliation grounded in established principles of pharmaceutical solid-state chemistry. The analysis emphasises on the observed XRD patterns and melting points on the polymorphs. All quantitative data points, including melting points (∘C), characteristic XRD 2θ angles, and qualitative information (compositional details and preparation methods), were systematically extracted and tabulated for better understanding.

4. RESULTS AND DISCUSSION

Table 1: Solid-state characteristics of Ferric Maltol Polymorph 'A'.

Characteristics	Polymorph 'A'
Composition	Pure API (with L-Lysine and ascorbic acid)
Melting Point	~300.2∘C
XRD 2θ Peaks	15.58∘ and 22.56∘ [1]

Table 2: Solid-state characteristics of Ferric Maltol Polymorph 'S'.

Characteristic	Polymorph 'S' (Patent)
Composition	Pure API (with L-Lysine and Ascorbic Acid)
Melting Point	276.56∘C
XRD 2θ Peaks	32∘ and 45.41∘ [2]

The data presented in the table highlights the distinct analytical characteristics of the designation of Ferric Maltol Polymorph 'A' representing the pure API standard.[16] Polymorph 'A' is characterized by the intrinsic thermal property of the pure, single-component Ferric Maltol crystal. Its recorded melting point is approximately 300.2∘ C. Furthermore, Polymorph 'A' exhibits a clear crystallographic fingerprint which consists of characteristic XRD 2-theta peaks at 15.58∘ and 22.56∘. These analytical values accurately reflect the unadulterated crystal lattice and serve as the regulatory standard for the pure API identity in quality control. Polymorph 'S' is reported with a lower melting point of 276.56∘ C and a unique set of XRD 2-theta peaks at 32∘ and 45.41∘.

Though Polymorph S exhibits different XRD peaks from that of Polymorph A; still, they are considered to be directly attributable to the presence of the co-processed excipients, the diffraction patterns of the excipients, or the unique co-crystal/co-processed interface formed between the API core and the stabilizing layers.[17] To maintain API Standard, Polymorph 'A' (with a melting point of ~300.2∘C and peaks at 15.58∘ and 22.56∘) must be maintained as the regulatory standard for the pure (API) identity.[18] Its analytical values confirm the integrity of the co-processing methodology designed to enhance stability and solubility.[19]

By formally establishing this scientific equivalence, WBCIL maintains a single, consistent polymorphic standard for Ferric Maltol, simplifying quality assurance and ensuring that stability and bioavailability claims are rooted in the well-characterized properties of the core 'A' crystal structure. WBCIL manufactures both Polymorph 'A' and Polymorph 'S' as per the requirement of the customers.

5. CONCLUSION

The study shows comprehensive analysis of the solid-state characteristics of Ferric Maltol Polymorph 'A' and Polymorph 'S'. Polymorph 'A' is definitively established as the intrinsic, pure API standard, characterized by a melting point of 300.2∘C and the genuine crystallographic fingerprint (XRD peaks at 15.58∘ and 22.56∘ 2-theta). This designation must serve as the primary regulatory standard for API identity within quality control frameworks. Polymorph 'S' shows a lower melting point and differing XRD profile to that of Polymorph A. Both the polymorphs contain the excipients L-Lysine and Ascorbic Acid.

By formally establishing Polymorph 'A' as the benchmark for the pure API, pharmaceutical manufacturers, such as WBCIL, can maintain a single, consistent polymorphic standard for Ferric Maltol. This rigorous scientific approach is essential for simplifying quality assurance, ensuring product integrity, and validating that all claims regarding stability and bioavailability are reliably rooted in the stable, well-characterized core 'A' crystal structure.

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